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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,387	03/06/2002	Naoki Midoh	2002-0317A	2875

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,387	MIDOH ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15* is/are pending in the application.

4a) Of the above claim(s) *2-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 15* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-13 and 15 are pending in the application.

[2] Applicants' amendment to the claims, filed 7/11/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Claims 2-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/18/2003.

[4] Claims 1, 13, and 15 are being examined on the merits.

[5] Applicants' arguments filed 7/11/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim to Priority

[7] Applicants' claim for foreign priority under 35 USC § 119(a)-(d) to applications JP 11253040, filed 9/7/1999 and JP 2000104291, filed 4/6/2000, is acknowledged. Certified copies of the foreign priority documents have been filed in the instant application on 3/6/2002. English language translations of the foreign priority documents have been filed in the instant application on 6/21/2004 and 11/3/2004.

Claim Objection

[8] Claim 1 is objected to in the recitation of the indefinite article "an" in the phrase "an amino acid sequence." Based on the prosecution history, it is clear that applicants intend to limit the polypeptide of claim 1 to a polypeptide comprising the entirety of the amino acid sequence of SEQ ID NO:2. For example, referring to claim 1 in its current form, applicants state, "amended claim 1 is directed to the protein of SEQ ID NO: 2" (p. 7, top of the response filed 11/3/2004). It is suggested that applicants replace the indefinite article "an" with "the" in the phrase "an amino acid sequence."

Claim Rejections - 35 USC § 112, First Paragraph

[9] The scope of enablement rejection of claims 13 and 15 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue the scope of variants of SEQ ID NO:2 as encompassed by the claims does not include a vast number, relying on Examples 9 and 10 of the Revised Interim Written Description Guidelines Training Material, Enzo Biochem, Inc. v. Gen-Probe Inc. 63 USPQ2d 1609, and Ex Parte Herrmann No. 2002-1630. According to applicants, there is no substantial variation within the scope of polypeptide sequences because the stringency of the recited hybridization conditions yields structurally similar molecules. Applicants argue that the stringent hybridization conditions would exclude the vast number of polypeptide variants as the corresponding nucleic acids encoding the variant polypeptides would not hybridize to SEQ ID NO:1 under the recited conditions. Applicants argue that

hybridization and screening techniques were well-known at the time of the invention and only routine experimentation is required to make all variants as encompassed by the claims. Applicants further argue that the Office has issued numerous patents with claims reciting "stringent conditions," thus allegedly demonstrating the PTO's acceptance of such language.

Applicants' argument is not found persuasive. The examiner does not dispute that, at the time of the invention, methods of hybridization were known in the art. Further, the examiner acknowledges that the specification discloses an assay for determining whether an encoded protein has PF1022 synthetase activity (pp. 21-22). However, that hybridization was known in the art at the time of the invention and that the specification discloses an activity assay is insufficient to enable the full scope of the claimed invention. Contrary to applicants' position, the claims encompass a vast number of polypeptide variants. In view of the disclosure of the specification, claims 13 and 15 broadly encompass all mutants and variants within the hybridization limitations of the claims. The specification provides not even a single working example of a variant of SEQ ID NO:1 that encodes a polypeptide having PF1022 synthetase activity. The examiner has provided objective evidence (see Branden et al., Witkowski et al., Seffernick et al., and Broun et al., all cited in the Office action mailed 3/9/2005) of the high level of unpredictability in altering an encoding nucleic acid sequence with an expectation of obtaining an encoded polypeptide having desired activity/utility. This evidence is undisputed by applicants. Neither the prior art nor the specification discloses guidance regarding those nucleotides of SEQ ID NO:1 or amino acids of SEQ

ID NO:2 that can be altered with an expectation of maintaining the ability to encode a polypeptide having the desired PF1022 synthetase activity. As the specification fails to provide any guidance as to those nucleotides of SEQ ID NO:1 or amino acids of SEQ ID NO:2 that can be altered without disrupting the desired activity, this is essentially a trial-and-error process. Based on the recited hybridization limitations, the examiner has used the well-known calculation of Meinkoth et al. (see, *e.g.,* US Patent 6,057,491, particularly column 7, lines 32-41) to estimate that parts (c) of claims 13 and 15 encompass nucleotide sequences that are 85% identical to SEQ ID NO:1 (assuming that for each 1 degree Celsius the Tm is reduced from that calculated for a 100% identity hybrid, the amount of mismatch permitted is increased by about 1%). Thus, in order to make the full scope of recited polypeptides, one can alter up to approximately 15% of the nucleotides of the sequence of SEQ ID NO:1, which is 1,444 nucleotides. As noted in a previous Office action, the resulting encoded polypeptide variants encompass those having a single amino acid substitution, addition, deletion, or insertion and any combination of amino acid substitutions, additions, deletions, and/or insertions up to the recited hybridization limitation. In this case, the coding region of SEQ ID NO:1 is over 9500 nucleotides in length, encoding a polypeptide that is 3210 amino acids in length. Although the claims are not limited to variants having only a single amino acid substitution, in order to generate only *single* amino acid variants of each amino acid of SEQ ID NO:2, one must make 19^{3210} or 6×10^{4104} variants – just for *single amino acid variants*. Thus, at a minimum, the number of variants is 19^{3210} and the number becomes seemingly infinite when one considers that the claims broadly encompass simultaneous

alteration of up to about 1444 nucleotides of the encoding nucleic acid sequence by substitution, addition, deletion, and/or insertion of a polypeptide that is 3210 amino acids. As SEQ ID NO:2 is encoded by 3210 codons and one can simultaneously alter up to 1444 nucleotides, at one nucleotide variation per codon, and assuming that each altered codon alters the corresponding amino acid, this allows for alteration of up to 45% of the amino acids of the polypeptide of SEQ ID NO:2. Based on this rough approximation, *the number of allowed permutations is astounding*. While methods to produce variants of a known sequence, e.g., site-specific mutagenesis and random mutagenesis, are well-known to the skilled artisan, producing variants having PF1022 synthetase activity requires that one of skill in the art know or be provided with guidance for the selection of which of the *at least* 19^{3210} variants has the desired activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the at least 19^{3210} possible variants. The reference of Guo et al. (*Proc Natl Acad Sci* 101:9205-9210) teaches a study suggesting that the percentage of variants having multiple substitutions that maintain activity appears to be exponentially related by the simple formula: $(.66)^x \times 100\%$ (where x is the number of mutations introduced).

As noted above, the claims broadly encompass a polypeptide that can have 45% of the amino acids altered, or another way of stating this is that the claims encompass polypeptides having 55% identity to SEQ ID NO:2. Applying this estimate to the instant protein, 55% identity to SEQ ID NO:2 allows up to 1444 mutations within the 3210 amino acids of SEQ ID NO:2 and thus only $(.66)^{1444} \times 100\%$ or 2.6×10^{-259} % of random mutants having 55% identity to SEQ ID NO:2 would be active. Thus, a significant

number of variants must be screened in order to isolate those variants of SEQ ID NO:2 having the desired PF1022 synthetase activity. The art clearly *does not* typically engage in the screening of 19^{3210} single amino acid variants (and it follows that the art does not typically engage in the screening of $>19^{3210}$ variants) to isolate those relatively few variants (2.6×10^{-259} %) that would have the desired activity. As such, based on a determination by weighing all of the factual considerations of In re Wands, the examiner has made a determination that the specification does not enable the claimed invention without undue experimentation.

In response to applicants' argument that the PTO has sanctioned such hybridization language, applicants are reminded that each patent application is examined on its merits and the facts in each application vary sufficiently such that applicants cannot make a generalization that claims reciting "stringent conditions" are generally accepted by the Office.

Conclusion

[10] Status of the claims:

- Claims 1-13 and 15 are pending.
- Claims 2-12 are withdrawn from consideration.
- Claim 1 is objected to for a minor grammatical issue, but would otherwise is in a condition for allowance.
- Claims 13 and 15 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Thurs and alternate Fri, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656